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APPLICATION NO. .	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/084,706	02/26/2002	Poul Baad Rasmussen	0228us410	7876

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MAXYGEN, INC.
INTELLECTUAL PROPERTY DEPARTMENT
515 GALVESTON DRIVE
RED WOOD CITY, CA 94063

EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT PAPER NUMBER

1647

DATE MAILED: 04/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/084,706

Applicant(s)

RASMUSSEN ET AL.

Examiner

Jegatheesan Seharaseyon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 January 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 88-108 is/are pending in the application.
- 4a) Of the above claim(s) 100-108 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 88-99 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 2/26/2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11/13/02 & 12/12/0.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 88-99, drawn to interferon- β in response filed 1/24/2005 is acknowledged.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Appropriate correction is required.

Priority

3. The Applicants are entitled to a priority date of 02/27/2001 based on the enabling disclosure of the provisional application 60/272,116.

Claim Rejections - 35 USC § 112, second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 88-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4a. Claim 88 is rejected as vague and indefinite for reciting the term "interferon β -activity" is not defined in the specification. Therefore the metes and bounds of these claims are unclear. Interferon β is known to have diverse activities such as antiviral, antiproliferative and immunomodulatory activities. It unclear what activity is

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contemplated in claim 88. Claims 89-99 are rejected insofar as they are dependent on the rejected claim.

Claim Rejections - 35 USC § 112, first paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5a. Claims 88-99 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a written description rejection.*

The specification discloses several potential interferon- β substitutions at wild-type positions including S2N+N4T+C17S+K19R+K33R+K45R+Q51N+E53T+F111N+R113T+K123R. This meets the written description and enablement provisions of 35 USC 112, first paragraph. However, the specification does not disclose all possible variants (with up to 15 amino acid residue changes) of interferon- β . Applicants have claimed a genus of polypeptides that have no common function (interferon- β has antiviral effects anti proliferative effects etc.). It is not clear what substitutions will retain common functions. It is also not clear how the changes to the polypeptide would affect the glycosylation. Furthermore, the specification fails to disclose if there are multiple glycosylation sites and how amino acid substitution next one site will affect the other etc. It is also not how and what functions will be affected by the glycosylation. To

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provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of SEQ ID number and some possible amino acid changes (amino acid changes at up to 15 positions). There is not even identification of any particular portion of the structure that must be conserved. The claims as written, however, encompass interferon- β variant sequences which were not originally contemplated and fail to meet the written description provision of 35 USC 112, first paragraph because the written description is not commensurate in scope with the recitation of claims 88-99. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of isolated interferon- β polypeptide with substitutions for example, at wild-type positions S2N+N4T+C17S+K19R+K33R+K45R+Q51N+

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E53T+F111N+R113T+K123R the skilled artisan cannot envision all the detailed chemical structure of the claimed polypeptides (with 15 possible amino acid changes), regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The polypeptide itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

Therefore, only the isolated interferon- β polypeptide with substitutions at wild-type positions S2N+N4T+C17S+K19R+K33R+K45R+Q51N+E53T+F111N+R113T+K123R but not the full breadth of the claims (with all 15 possible amino acids changed) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. As a result, it does not appear that the inventors were in possession of various polypeptide sequences set forth in claims 88. Claims 89-99 are rejected insofar as they depend on rejected claim 88.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

5b. Claims 88-99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an interferon- β variant, with substitutions at

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K19R+K45R+K123R of the wild type protein which has antiviral activity (see page 107 of the specification), the disclosure does not reasonably provide enablement for all variants interferon- β contemplated. In addition, it is also unclear what activity if any will be associated with the specific interferon- β variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Despite knowledge in the art for producing variants of a given polypeptide with amino acid deletions, insertions or substitutions the specification fails to provide any guidance regarding the changes/modifications contemplated and yet retain the function(s) of the interferon- β variants claimed. Furthermore, detailed information regarding the structural and functional requirements of the disclosed variant protein is lacking. Although it is accepted that the amino acid sequence of a polypeptide

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determines its structural and functional properties, predicting a protein's structure and function from mere sequence data remains an elusive task. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex.

While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, *Biochemistry* 29:8509-8517; Ngo et al., 1994, *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were

identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The instant disclosure fails to disclose which if any functions of the interferon- β activities will remain or required after the mutation of the polypeptide. It is also unclear what are functions that will be enhanced following the glycosylation of interferon- β . Therefore, predicting which variants would retain the functions of the protein is well outside the realm of routine experimentation. Thus, undue amount of experimentation would be required to generate changes/modifications contemplated and yet retain the function of the proteins claimed.

Applicants have not taught how one of skill in the art would use the full scope of polypeptide sequences encompassed by the invention of claims 88-99. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed sequences. The amount of experimentation required to make and/or use the full scope of the claimed sequences would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 88-99 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior art of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

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6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bentzien (U. S. Patent No. 6, 514, 729) describes interferon- β muteins. It also describes glycosylated variants. However, it does describe an amino acid substitution at position -1 relative to at least one of the N-glycosylation site(s).


7. No claims are allowable.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


JANET ANDRES
PRIMARY EXAMINER